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Clinical Management of Nonpalpable or Small Breast Masses by Fine-Needle Aspiration Biopsy (FNAB) Under Ultrasound Guidance

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Background and Objectives: Open breast biopsy of palpable breast masses is widely accepted. Now, the use of high-resolution, real-time ultrasound (US) makes it easy to detect nonpalpable or small breast nodules, as well as palpable breast masses.

Methods: We performed fine-needle aspiration biopsy (FNAB) under US guidance to manage the nonpalpable or small breast masses detected by US examination and to distinguish between benign and malignant tumors. To investigate the usefulness and sensitivity of FNAB under US guidance, we reviewed a total of 137 FNAB records for cases diagnosed between January 1993 and December 1994.

Results: Fifty-five cases were classified as benign, 70 as atypical/indeterminate, 1 as suspicious/probably malignant, 6 as malignant, and 5 as unsatisfactory. Of these, five cases were confirmed as malignant, but one case showed no malignancy at surgery. Four cases were nonpalpable breast cancer, two were in stage 0, and two were in stage I. One case in the suspicious/probably malignant group on the initial FNAB was shown to be malignant by re-aspiration on follow-up study. The sensitivity of FNAB under US guidance was 83.3% (5/6) and the specificity was 99.2% (125/126). The diagnostic accuracy was 83.3% (5/6) and the negative predictive value was 99.2% (125/126).

Conclusions: FNAB under US guidance is useful for the management of nonpalpable or small breast masses; it is sensitive for distinguishing between benign and malignant tumors and may reduce unnecessary surgical procedures and replace conventional manual aspiration biopsy.

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KEY WORDS: **breast cancer; fine needle aspiration biopsy (FNAB) under ultrasound guidance; ultrasound (US); diagnostic accuracy; sensitivity and specificity**

INTRODUCTION

Breast cancer is the most frequent type of cancer encountered among women in the United States [1]. In Japan, the mortality and incidence of breast cancer are relatively low compared with the United States. The mortality, however, of this cancer in Japan has gradually been increasing, and this disease will become a leading cancer in the near future [2]. Recent advances in breast imaging have improved the detection rate for breast can-

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cer, especially that of early, small and nonpalpable cancer [3–5].

The technique of fine-needle aspiration biopsy (FNAB) has brought the benefits of rapid diagnosis, minimal disruption of the tumor beds, and low cost [6–8]. However, the diagnostic accuracy of FNAB is variable, and this manual technique has not been universally accepted. A large part of the problem with the procedure is the false-negative sampling, often due to uncertain placement of the needle [9–11].

High-resolution, real-time ultrasound (US) examination of the breast improved the detection of small or nonpalpable breast cancers [12,13] revealing tumors that could not be detected solely by physical examination or mammography [13,14]. This raises the question of how to manage small or nonpalpable breast lesions detected by US. We have been performing FNAB under US guidance for US-detected nonpalpable or small breast masses. FNAB under US guidance was first reported in 1987 [15]. There are few reports, however, on the usefulness of FNAB under US guidance [16–18] and there has been no report of clinical management of nonpalpable or small mases based on FNAB under US guidance.

In the present study, we evaluated our records to investigate the usefulness and sensitivity of FNAB under US guidance for clinically occult small or nonpalpable breast masses as well as palpable breast masses. Furthermore, we assessed the management of these tumors by FNAB under US guidance.

MATERIALS AND METHODS

Case records of 137 consecutive patients who underwent FNAB under US guidance between January 1993 and December 1994 were evaluated. All records were available and complete. All 137 patients were examined by US at the Health Care Center, Yamanashi Prefectural Welfare Federation of Agricultural Co-operatives, and demonstrated US findings such as hypoechoic mass with irregular margin or with internal heterogeneity, except for pure cyst, as described previously [12]. Patient age ranged from 22 to 70 years. The average age was 47.6 years with a standard deviation of 9.4 years.

The US apparatus was the SSD650CL or 1200 (Aloka, Tokyo, Japan) with a high-frequency, real-time 10-MHz mechanical sector type transducer. We performed FNAB, using a 21-gauge needle and disposable syringe (Hakko, Tokyo, Japan) equipped with a transducer by an attachment apparatus. In the local skin anesthetized condition, the needle was inserted obliquely along a path parallel to the scanning plane with the mass located in the center. Aspiration was performed using a to-and-fro movement and rotation of the needle, when the needle tip reached the center of the target. All needle movements were visualized on a real-time US image. The aspirated sample was ejected onto slide glass, spread thinly, and immediately wet-fixed in ethanol. The smears were assessed by a consultant cytopathologist and classified according to diagnostic terminology as described elsewhere [19]. For *benign* smears, patients are followed once a year for 2 years. For *atypical/indeterminate* smears, patients are followed every 6 months for 2 years. For *suspicious/probably malignant and malignant* smears, patients require immediate confirmation. When cytological classification could not be determined due to an inadequate specimen showing no normal or abnormal cells, patients were classified as unsatisfactory and told to return several days later for re-aspiration. Follow-up study was carried out by physical examination, US examination, or mammography. When the followed-up lesion showed changes compared with previous findings, FNAB was performed.

TABLE I. Distribution of Cytological Findings of Fine-Needle Aspiration Biopsy Specimens (N = 137)

Classification	No.
Benign	55
Atypical/indeterminate	70
Suspicious/probably malignant	1
Malignant	6
Unsatisfactory	5

Staging for breast cancer was done according to the American Joint Commission on Cancer Staging [20]. True-positive, false-negative, true-negative, and false-positive diagnoses were determined for both benign and malignant lesions. All false diagnoses were determined by strict follow-up study, re-evaluation by US or re-FNAB, and surgical procedures. In brief, false-negative cases were defined as the presence of malignant cells on follow-up study, because only suspicious/probably malignant or malignant cases underwent immediate surgery. False-positive cases were determined by the absence of malignancy in the surgical specimen.

RESULTS

The cytological classification is summarized in Table I. Fifty-five cases were classified as benign, 70 as atypical/indeterminate, 1 as suspicious/probably malignant, and 6 as malignant. In five cases, there were no cytological findings due to an inadequate specimen. However, re-aspiration was performed, resulting in reclassification as benign. Among the 70 atypical/indeterminate cases, 21 cases were cytologically diagnosed as mastopathy, 24 cases as fibroadenoma, and 6 as apocrine cyst, since each lesion contained atypical cells. In the other 19 cases, there was not enough material to diagnose definitively, but the cellular findings revealed atypia. One case classified as suspicious/probably malignant was cytologically diagnosed as papillary tumor on the initial FNAB. On follow-up study, re-aspiration revealed ma-

TABLE II. Details of the 5 Breast Cancers Confirmed by Fine-Needle Aspiration Biopsy

Case no.	Age (yr)	Palpation[a]	Tumor size[b] (cm)	T	N	M	Stage
1	43	Non	1.1 × 0.5	T1c	N0	M0	I
2	45	Pal	2.0 × 1.0	T2	N0	M0	IIa
3	49	Non	0.5 × 0.5	Tis	N0	M0	0
4	66	Non	0.6 × 0.5	T1b	N0	M0	I
5	51	Non	0.8 × 0.5	Tis	N0	M0	0

[a]Non and Pal indicate non-palpable and palpable, respectively.
[b]Tumor size was measured by US, transverse × longitudinal size.

TABLE III. Sensitivity and Specificity of Fine-Needle Aspiration Biopsy (FNAB) in Benign and Malignant Diagnoses

	FNAB (no.)	
Malignancy	Positive	Negative
Present	5	1
Absent	1	125 (5)[a]

[a]Number in parenthesis indicates inadequate specimen on the initial FNAB.

lignancy in the form of papillary adenocarcinoma. Six cases, which were classified as malignant, underwent surgery.

Details of the five breast cancers are shown in Table II. The sixth malignant case was diagnosed as intraductal papilloma by microscopic examination of the resected specimen. The average age was 50.8 years with a standard deviation of 9.0 years. One tumor was palpable, and four were nonpalpable. The nonpalpable tumors were detected by US examination only, and three of six tumors measured less than 1.0 cm. According to the TNM staging system, two cancers were in stage 0, two in stage I, and one in stage IIa.

The numbers of true-positive, false-positive, false-negative, and true-negative cases were 5, 1, 1, and 125, respectively. Although five cases were classified as unsatisfactory due to an inadequate specimen obtained on the initial aspiration, re-aspiration showed them to be benign. Therefore, we included these in the true-negative category. The sensitivity was 83.3% (5/6), specificity 99.2% (125/126), diagnostic accuracy 83.3%, and negative predictive value 99.2% (125/126).

DISCUSSION

High-resolution real-time US has allowed detection of many small and nonpalpable breast masses, and subsquent management [12]. FNAB under US guidance is safe, minimally invasive, and inexpensive. In the present study, we showed that this technique is useful and sensitive for the diagnosis and management of small and nonpalpable breast masses. A few investigators have reported on the accuracy and clinical usefulness of this technique [16–18]. However, previous studies did not describe the management of breast masses and staging of cancer. Of the five aspirated breast cancers, four were nonpalpable tumors, two were in stage 0, and two were in stage I. Three nonpalpable tumors could not be visualized by preoperative mammography, mainly because of the density of breast tissue. Tumors in dense breasts have been detected by US [13,14], and the present study also indicated that small tumors could be managed by FNAB under US guidance. Our study also showed that the minimum size for aspiration was 0.5 × 0.5 cm measured by US in stage 0, allowing subsequent cytological diagnosis. However, a larger number of true-positive and false-positive diagnoses of carcinoma would be needed to establish a minimum size for successful aspiration.

FNAB has conventionally been performed manually without imaging guidance. Several studies have shown that conventional FNAB provides a sensitivity of 53–99%, a specificity of 99–100%, and an accuracy of 76–99% [21,22]. Clearly, size and location of tumors and training skill and experience of aspirators are important factors in the failure or success of manual aspiration biopsy of palpable lesions. Our study showed a sensitivity of 83.3% (5/6), a specificity of 99.2% (125/126), a and diagnostic accuracy of 83.3% with US-guided FNAB. Hatada et al. reported a sensitivity of 89.3%, a specificity of 82.9%, and an accuracy of 86.9%, using the same method. Thus the sensitivity and accuracy of this method were comparable to those of the conventional method [18]. Their study was conducted almost coincidental with ours, but with a slightly different design. Their study was based on preoperative investigations in a hospital, whereas ours was done in a general clinic. In other words, there would be some selection bias toward suspicious lesions in their situation. For these reasons, we could not precisely compare the results. Gordon et al. also reported that the sensitivity of FNAB under US guidance was 95%, the specificity was 92%, and the accuracy was 93% [17]. These results were splendid. The false-positive and false-negative cases in our series involved papillary tumors, suggesting the difficulty of cytological diagnosis of this type of tumor and the need for special consideration of papillary lesions. Such problems appeared to be unavoidable and become statistically prominent in a study involving a relatively small number of patients. Like manual FNAB, US-guided biopsies are operator dependent. Further training in this sampling technique and accumulation of experience with a large volume of cases would probably improve the sensitivity, specificity, and accuracy of US-guided biopsies.

False-positive rates of FNAB had varied from 0% to 5%, and false-negative rates ranged from 0% to 35% [9]. In our study, the false-positive rate was 0.7% and the false-negative rate was 0.7%. There was one false-positive case in this study. This case was cytologically

diagnosed as papillary adenocarcinoma. Histopathological examination of the surgical specimen, however, revealed intraductal papilloma without any sign of malignancy. This case illustrates the difficulties inherent in cytological diagnosis, which limit the benefit of aspiration cytology for the diagnosis of these lesions [23,24]. There was also one false-negative case, which was diagnosed as papillary tumor on the initial FNAB. Three months later, follow-up aspiration revealed papillotubular adenocarcinoma. Although in this study, false-negative cases were defined as the presence of malignant cells on the follow-up study, a true result appeared to be unclear, because all aspirated lesions of the breast could not be removed by open biopsy. The false-negative diagnosis has become a major concern among those practicing aspiration cytology of the breast [10,11]. Most false-negative diagnoses appear to be due to technical causes, resulting in overinterpretation of inadequate or unsatisfactorily prepared material [9,11,25]. In the present study, 19 cases in the atypical/indeterminate class could not be diagnosed definitively, due to low cellularity. However, there was no evidence of malignancy after 2 years of follow-up US examination every 6 or 12 months after FNAB. Layfield et al. recently reported that the use of cell quantitation would decrease the false-negative rate of sampling in epithelial lesions of the breast [26]. Their study, however, showed the false-negative rate of palpable lesions by using manual aspiration biopsy, whereas ours did the same for palpable and nonpalpable lesions using US-guided aspiration biopsy. Thus we could not compare these results precisely. Based on accumulation of data for US-guided FNAB, the false-negative rate should be investigated using the cell quantitation method. These results indicate low false-positive and false-negative rates of FNAB under US guidance, the need for caution with papillary lesions, and the need for ongoing extended experience by aspirators and cytopathologists to obtain superior results.

Strictly speaking, false cases should be determined by open biopsy and subsequent histological diagnosis. In the present study, however, false-negative cases were defined as the presence of malignant cells on follow-up study. Follow-up periods were every 6 months for indeterminate atypical cases and once a year for benign cases for 2 years, since we considered that the indeterminate atypical group requires more frequent follow-up than patients with a benign diagnosis. According to National Cancer Institute recommendations [19], the cytological diagnosis from FNAB should be correlated with the clinical and imaging characteristics, and patient management should be based on a triple test. Furthermore, mixed or inconclusive triplets have been recommended for excisional biopsy [19]. In our series, 70 atypical/indeterminate cases did not have US imaging characteristics and gave no clinical impression of malignancy. Atypical/indeterminate cases were treated by follow-up instead of open biopsy, since the characteristics of these lesions could be easily detected by US and most of them were small and nonpalpable nodules. We considered that a surgical procedure was not always necessary until a US image showed the characteristic changes of these nodules such as an increase in tumor size. Indeed, 70 indeterminate atypical cases did not reveal malignancy during the follow-up period. A longer follow-up period would be needed to ensure an accurate assessment of these nodules as benign.

Small or nonpalpable breast masses, as well as palpable masses, were managed by US and FNAB under US guidance, since our follow-up study did not reveal malignancy in benign and atypical/indeterminate classes. These results suggested that unnecessary surgical procedures such as open breast biopsy and manual aspiration biopsy could be reduced and replaced by FNAB under US guidance. There were no major complications in this series, and the procedure was well tolerated by patients. Cost effectiveness was an unresolved issue in this study. However, determination of the appropriate duration of the follow-up period for benign and atypical/indeterminate lesions would clarify the cost burden. Recently, core needle biopsy of radiologically detected breast lesions ha offered an attractive alternative to the surgical procedure in the United States [27,28]. Comparative study of FNAB and core biopsy is required to improve the management of nonpalpable or small breast lesions further. We consider that FNAB under US guidance can contribute to the diagnosis of nonpalpable early breast cancer, management of breast masses, reduction of unnecessary surgical procedures, and replacement of conventional manual aspiration biopsy.

CONCLUSIONS

FNAB under US guidance is useful for the management of nonpalpable or small breast masses, is sensitive for distinguishing between benign and malignant tumors, and may reduce unnecessary surgical procedures and replace conventional manual aspiration biopsy.

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